

WHAT IS CLAIMED IS:

I. 1. A composition comprising:
a mixture formed by mixing ingredients comprising a growth
factor related to epithelial cell function and an extracellular matrix-degrading
5 protease enzyme.

2. The composition of claim 1, wherein the growth factor related to
epithelial cell function comprises a fibroblast growth factor ("FGF") or
functional biological equivalent thereof.

10 3. The composition of claim 1, wherein the growth factor related to
epithelial cell function comprises keratinocyte growth factor ("KGF") or
functional biological equivalent thereof.

15 4. The composition of claim 1, wherein the growth factor related to
epithelial cell function comprises epidermal growth factor ("EGF"), dN23KGF,
KGF-2, acidic fibroblast growth factor ("aFGF"), transforming growth factor- α
("TGF- α "), transforming growth factor- β ("TGF- β "), insulin-like growth
factor-I ("IGF-I"), hepatocyte growth factor ("HGF"), or a functional biological
equivalent thereof.

20 5. The composition of claim 1, wherein the extracellular matrix-
degrading protease enzyme comprises an enzyme related to plasmin,
plasminogen or functional biological equivalent thereof.

6. The composition of claim 1, wherein the extracellular matrix-
degrading protease enzyme comprises a plasmin, or functional biological
equivalent thereof.

7. The composition of claim 1, wherein the extracellular matrix-degrading protease enzyme comprises a plasminogen, or functional biological equivalent thereof.

5 8. The composition of claim 1, wherein the extracellular matrix-degrading protease enzyme comprises a miniplasmin, a miniplasminogen, or functional biological equivalent thereof.

9. The composition of claim 1, wherein the extracellular matrix-degrading protease enzyme comprises a microplasmin, a microplasminogen, or functional biological equivalent thereof.

10 10. The composition of claim 1, wherein the extracellular matrix-degrading protease enzyme comprises a trypsin, a metalloprotease, a collagenase, or functional biological equivalent thereof.

15 11. The composition of claim 1, wherein the extracellular matrix-degrading protease enzyme comprises a plasminogen activator, or functional biological equivalent thereof.

12. The composition of claim 11, wherein the plasminogen activator comprises urokinase plasminogen activator (uPA), tissue plasminogen activator (tPA), streptokinase or functional biological equivalent thereof.

20 13. A composition comprising:
a mixture formed by mixing ingredients comprising a fibroblast growth factor and an extracellular matrix-degrading protease enzyme.

14. The composition of claim 13, wherein the fibroblast growth factor comprises keratinocyte growth factor ("KGF") or functional biological equivalent thereof.

15. The composition of claim 13, wherein the extracellular matrix-degrading protease enzyme comprises an enzyme related to plasmin, plasminogen or functional biological equivalent thereof.



5 16. The composition of claim 13, wherein the extracellular matrix-degrading protease enzyme comprises a plasmin, or functional biological equivalent thereof.



17. The composition of claim 13, wherein the extracellular matrix-degrading protease enzyme comprises a plasminogen, or functional biological equivalent thereof.

10 18. The composition of claim 13, wherein the extracellular matrix-degrading protease enzyme comprises a miniplasmin, a miniplasminogen, or functional biological equivalent thereof.

19. The composition of claim 13, wherein the extracellular matrix-degrading protease enzyme comprises a microplasmin, a microplasminogen, or functional biological equivalent thereof.

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20. The composition of claim 13, wherein the extracellular matrix-degrading protease enzyme comprises a trypsin, a metalloprotease, a collagenase, or functional biological equivalent thereof.

21. The composition of claim 13, wherein the extracellular matrix-degrading protease enzyme comprises a plasminogen activator, or functional biological equivalent thereof.

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22. The composition of claim 21, wherein the plasminogen activator comprises urokinase plasminogen activator (uPA), tissue plasminogen activator (tPA), streptokinase or functional biological equivalent thereof.

23. The composition of claim 13, wherein the fibroblast growth factor has a concentration of from 0.00001% [w/v] to 0.1% [w/v], and the extracellular matrix-degrading protease enzyme has a concentration of from 0.0001 [w/v] to 1% [w/v].

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24. The composition of claim 13 further comprising a carrier. (4)

25. The composition of claim 24, wherein the carrier comprises a buffer, a saline solution, a thickener, an emulsion, or an ointment. (4)

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26. A kit comprising:
a first component comprising a growth factor related to epithelial cell function in a first carrier in a first container; and a second component comprising an extracellular matrix-degrading protease enzyme in a second carrier in a second container. (4)

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27. The kit of claim 26, wherein the growth factor related to epithelial cell function comprises fibroblast growth factor ("FGF"), or functional biological equivalent.

28. The kit of claim 26, wherein the growth factor related to epithelial cell function comprises keratinocyte growth factor ("KGF"), or functional biological equivalent.

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29. The kit of claim 26, wherein the extracellular matrix-degrading protease enzyme comprises an enzyme related to plasmin, plasminogen or functional biological equivalent.

30. The kit of claim 26, wherein the extracellular matrix-degrading protease enzyme comprises a plasmin, or functional biological equivalent.

31. The kit of claim 26, wherein the extracellular matrix-degrading protease enzyme comprises a plasminogen, or functional biological equivalent.

5 32. The kit of claim 26, wherein the extracellular matrix-degrading protease enzyme comprises a miniplasmin, a miniplasminogen, or functional biological equivalent.

33. The kit of claim 26, wherein the extracellular matrix-degrading protease enzyme comprises a microplasmin, a microplasminogen, or functional biological equivalent.

10 34. The kit of claim 26, wherein the extracellular matrix-degrading protease enzyme comprises a trypsin, a metalloprotease, a collagenase, or functional biological equivalent.

35. The kit of claim 26, wherein the extracellular matrix-degrading protease enzyme comprises a plasminogen activator, or functional biological equivalent.

15 36. The kit of claim 35, wherein the plasminogen activator comprises urokinase plasminogen activator (uPA), tissue plasminogen activator (tPA), a streptokinase, or functional biological equivalent.

37. The kit of claim 26, wherein the first carrier is the same as or different from the second carrier.

20 38. The kit of claim 26, wherein the first carrier comprises water, a buffer, a saline solution, a thickener, an emulsion, or an ointment. (4)

39. The kit of claim 26, wherein the second carrier comprises water, a buffer, a saline solution, a thickener, an emulsion, or an ointment. (4)

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40. A kit comprising:
a first component comprising a growth factor related to epithelial cell function in a first container;
a second component comprising an extracellular matrix-degrading protease enzyme in second container; and
a third component comprising a carrier in a third container.

41. The kit of claim 40, wherein the growth factor related to epithelial cell function comprises fibroblast growth factor ("FGF"), or functional biological equivalent.

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42. The kit of claim 40, wherein the fibroblast growth factor comprises keratinocyte growth factor ("KGF"), or functional biological equivalent.

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43. The kit of claim 40, wherein the extracellular matrix-degrading protease enzyme comprises an enzyme related to plasmin, plasminogen or functional biological equivalent.

44. The kit of claim 40, wherein the extracellular matrix-degrading protease enzyme comprises a plasmin, or functional biological equivalent.

45. The kit of claim 40, wherein the extracellular matrix-degrading protease enzyme comprises a plasminogen, or functional biological equivalent..

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46. The kit of claim 40, wherein the extracellular matrix-degrading protease enzyme comprises a miniplasmin, a miniplasminogen, or functional biological equivalent.

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47. The kit of claim 40, wherein the extracellular matrix-degrading protease enzyme comprises a microplasmin, a microplasminogen, or functional biological equivalent.

48. The kit of claim 40, wherein the extracellular matrix-degrading protease enzyme comprises a trypsin, a metalloprotease, a collagenase, or functional biological equivalent.

5 49. The kit of claim 40, wherein the extracellular matrix-degrading protease enzyme comprises a plasminogen activator, or functional biological equivalent.

50. The kit of claim 49, wherein the plasminogen activator comprises urokinase plasminogen activator (uPA), tissue plasminogen activator (tPA), a streptokinase, or functional biological equivalent.

10 51. The kit of claim 40, wherein the carrier comprises a buffer, a saline solution, a thickener, an emulsion, or an ointment.

52. A method of treating an injury in an animal or human, comprising:
applying to the injury a composition comprising a mixture
15 formed by mixing ingredients comprising a growth factor related to epithelial cell function and an extracellular matrix-degrading protease enzyme.

53. The method of claim 52, wherein the growth factor related to epithelial cell function comprises a fibroblast growth factor ("FGF") or functional biological equivalent thereof.

20 54. The method of claim 52, wherein the growth factor related to epithelial cell function comprises keratinocyte growth factor ("KGF") or functional biological equivalent thereof.

25 55. The method of claim 52, wherein the growth factor related to epithelial cell function comprises epidermal growth factor ("EGF"), dN23KGF, KGF-2, acidic fibroblast growth factor ("aFGF"), transforming growth factor- α

("TGF- α "), transforming growth factor- β ("TGF- β "), insulin-like growth factor-I ("IGF-I"), hepatocyte growth factor ("HGF"), or a functional biological equivalent thereof.

5 56. The method of claim 52, wherein the extracellular matrix-degrading protease enzyme comprises an enzyme related to plasmin, plasminogen or functional biological equivalent thereof.

57. The method of claim 52, wherein the extracellular matrix-degrading protease enzyme comprises a plasmin, or functional biological equivalent thereof.

10 58. The method of claim 52, wherein the extracellular matrix-degrading protease enzyme comprises a plasminogen, or functional biological equivalent thereof.

15 59. The method of claim 52, wherein the extracellular matrix-degrading protease enzyme comprises a miniplasmin, a miniplasminogen, or functional biological equivalent thereof.

60. The method of claim 52, wherein the extracellular matrix-degrading protease enzyme comprises a microplasmin, a microplasminogen, or functional biological equivalent thereof.

20 61. The method of claim 52, wherein the extracellular matrix-degrading protease enzyme comprises a trypsin, a metalloprotease, a collagenase, or functional biological equivalent thereof.

62. The method of claim 52, wherein the extracellular matrix-degrading protease enzyme comprises a plasminogen activator, or functional biological equivalent thereof.

63. The method of claim 62, wherein the plasminogen activator comprises urokinase plasminogen activator (uPA), tissue plasminogen activator (tPA), streptokinase or functional biological equivalent thereof.

5 64. The method of claim 52, wherein the injury involves cells of epithelial origin, comprising those in or on skin, oral cavity, digestive track, muscosal surface, eye, or lung.

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65. The method of claim 52, wherein the injury involves other cell types that growth factors also affect, comprising endothelial, fibroblast, or hepatocyte cells.

10 66. A method of treating an injury in an animal or human, comprising:

applying to the injury two components:

(a) growth factor related to epithelial cell function; and

(b) an extracellular matrix-degrading protease enzyme,

15 wherein component (b) is applied subsequent to component (a), or component (a) is applied subsequent to component (b).

67. The method of claim 66, wherein the growth factor related to epithelial cell function comprises a fibroblast growth factor ("FGF") or functional biological equivalent thereof.

20 68. The method of claim 66, wherein the growth factor related to epithelial cell function comprises keratinocyte growth factor ("KGF") or functional biological equivalent thereof.

5 69. The method of claim 66, wherein the growth factor related to epithelial cell function comprises epidermal growth factor ("EGF"), dN23KGF, KGF-2, acidic fibroblast growth factor ("aFGF"), transforming growth factor- α ("TGF- α "), transforming growth factor- β ("TGF- β "), insulin-like growth factor-I ("IGF-I"), hepatocyte growth factor ("HGF"), or a functional biological equivalent thereof.

70. The method of claim 66, wherein the extracellular matrix-degrading protease enzyme comprises an enzyme related to plasmin, plasminogen or functional biological equivalent thereof.

10 71. The method of claim 66, wherein the extracellular matrix-degrading protease enzyme comprises a plasmin, or functional biological equivalent thereof.

15 72. The method of claim 66, wherein the extracellular matrix-degrading protease enzyme comprises a plasminogen, or functional biological equivalent thereof.

73. The method of claim 66, wherein the extracellular matrix-degrading protease enzyme comprises a miniplasmin, a miniplasminogen, or functional biological equivalent thereof.

20 74. The method of claim 66, wherein the extracellular matrix-degrading protease enzyme comprises a microplasmin, a microplasminogen, or functional biological equivalent thereof.

75. The method of claim 66, wherein the extracellular matrix-degrading protease enzyme comprises a trypsin, a metalloprotease, a collagenase, or functional biological equivalent thereof.

76. The method of claim 66, wherein the extracellular matrix-degrading protease enzyme comprises a plasminogen activator, or functional biological equivalent thereof.

5 77. The method of claim 66, wherein the plasminogen activator comprises urokinase plasminogen activator (uPA), tissue plasminogen activator (tPA), streptokinase or functional biological equivalent thereof.

Table 1. The N-terminal sequence of the KGF cleavage fragment generated by trypsin, plasmin, and chymotrypsin.

Enzymes	N-terminal sequences of cleavage fragments*	Initial Yield (pmole)	Repetitive yield (%)
Plasmin	S-Y-D-Y-M	2.6	88.3
Trypsin	S-Y-D-Y-M	9.7	88.2
Chymotrypsin	D-Y-M-E-G	3.19	ND

* Each of the sequences is only found in one place over the entire KGF amino acid sequence (163 amino acids). See Fig. 2 for their positions in the sequence. ND, not determined.

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